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ABSTRACT

Distribution of cephalothin and cephaloridine in renal lymph is compared with penicillin G. Following intravenous infusion, cephaloridine is found in higher concentrations in renal lymph than in the corresponding plasma. Penicillin G levels in plasma, urine, and renal lymph vary, depending on the rate of infusion. Plasma levels, however, are higher than corresponding lymph levels. Penicillin G and cephalothin appear to be similarly handled by the kidney. Nalidixic acid is compared with nitrofurantoin. Renal handling of these antimicrobials is discussed. The importance of renal lymph concentrations of antibiotics in treatment of pyelonephritis is emphasized.

One of the most important clinical decisions in treating pyelonephritis is the selection of effective antibiotic agents. The agent of choice must be based on careful bacteriologic screening followed by the performance of sensitivity studies. A second important consideration is the selection of a therapeutic agent which will diffuse into the renal interstitium in biologically active form. Pyelonephritis begins in the interstitium, and the inflammatory process becomes multifocal if left untreated. Antimicrobials which are selectively reabsorbed by the renal tubules should probably be employed in the earliest periods of infection since these drugs concentrate within the renal interstitial spaces.

The importance of obtaining adequate antibiotic blood levels in gauging the effectiveness of treatment has been stressed by a number of established clinicians. Recently Stamey (1) has emphasized the importance of adequate urinary concentrations to eradicate the urinary tract of significant infection. Our studies in the past three years (2–5) have stressed the importance of renal tissue levels—renal lymph concentrations of antibacterials in assessing the adequacy of therapy. Observation of pyelonephritic changes occurring mainly in lymph capillaries of the interstitium during the early stages is probably significant.

The purpose of our studies is to compare the intrarenal distribution of three structurally related antibiotics; comparisons between plasma, urine, and renal lymph are made. A second objective is to report the distribution of nalidixic

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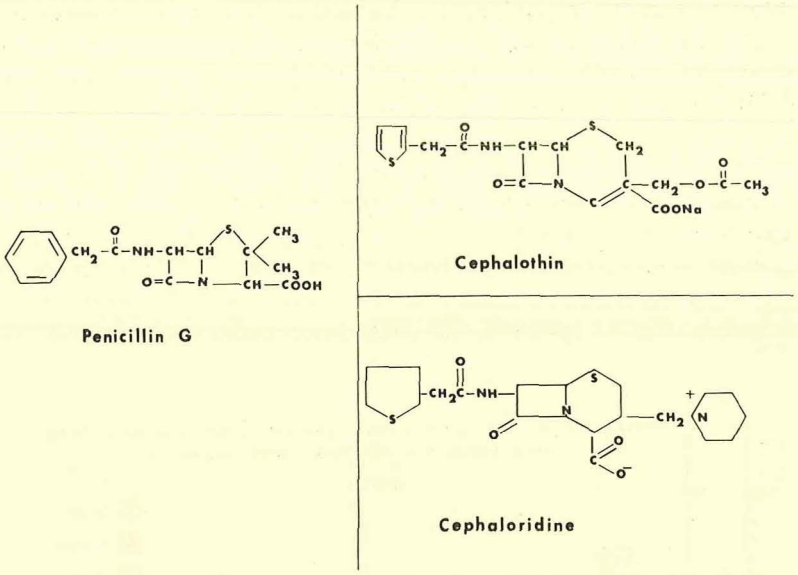

FIG. 1. Structural formulae of penicillin G, cephalothin, and cephaloridine

acid in renal lymph, plasma, and urine. Its distribution is compared with another common urinary antiseptic, nitrofurantoin.

MATERIALS AND METHODS

Mongrel dogs underwent renal exploration following pentobarbital anesthesia. Renal capsular or hilar lymphatic vessels were cannulated with polyethylene tubing for lymph samples. Corresponding samples of peripheral blood and urine were obtained for comparison.

Penicillin G (12,000 μg per kg), cephalothin[1] (46 mg per kg), or cephaloridine (47 mg per kg) was injected intravenously into an animal. One animal was employed for each antibiotic. Biologic samples were collected 1 to 6 hr following drug infusion.

Penicillin G, caphalothin, and cephaloridine were analyzed by the cup-plate assay technique using *Sarcina lutea* organisms previously poured into the media. Turbidity in the media, rather than number of organisms, was used in the preparation of the assay plate.

Nalidixic acid was administered by gastric tube (50 mg per kg). Biologic samples were obtained 1 to 4 hours after drug administration and were frozen. Nalidixic acid was analyzed at a later date by the method of McChesney et al. (6). Results obtained were compared with previously published data on the urinary antiseptic, nitrofurantoin.

RESULTS

Figure 1 depicts the structural formula of three antibiotics—penicillin G, cephalothin, and cephaloridine. Similarities can be seen.

[1] Cephalothin and cephaloridine were generously supplied through the courtesy of Dr. R. S. Griffith of the Lilly Laboratories for Clinical Research.

Penicillin G (12,000 μg per kg) was infused intravenously in separate dogs at two rates. In Figure 2*A* and *B*, penicillin was rapidly injected as a bolus. Distribution of penicillin in renal capsular lymph, plasma, and urine is plotted. Decreasing levels of the antibiotic are seen in urine, plasma, and lymph.

Penicillin G was infused (12,000 μg per kg) over a 4-hr period (Fig. 3). Renal lymph, plasma, and urine are compared. In a typical experiment the urine concentrations of penicillin increased progressively over the 5-hr collection period. Renal lymph levels, however, are $\frac{1}{5}$ to $\frac{1}{10}$ of the corresponding plasma concentration.

A bar graph (Fig. 4) compares the peak concentrations of penicillin G from

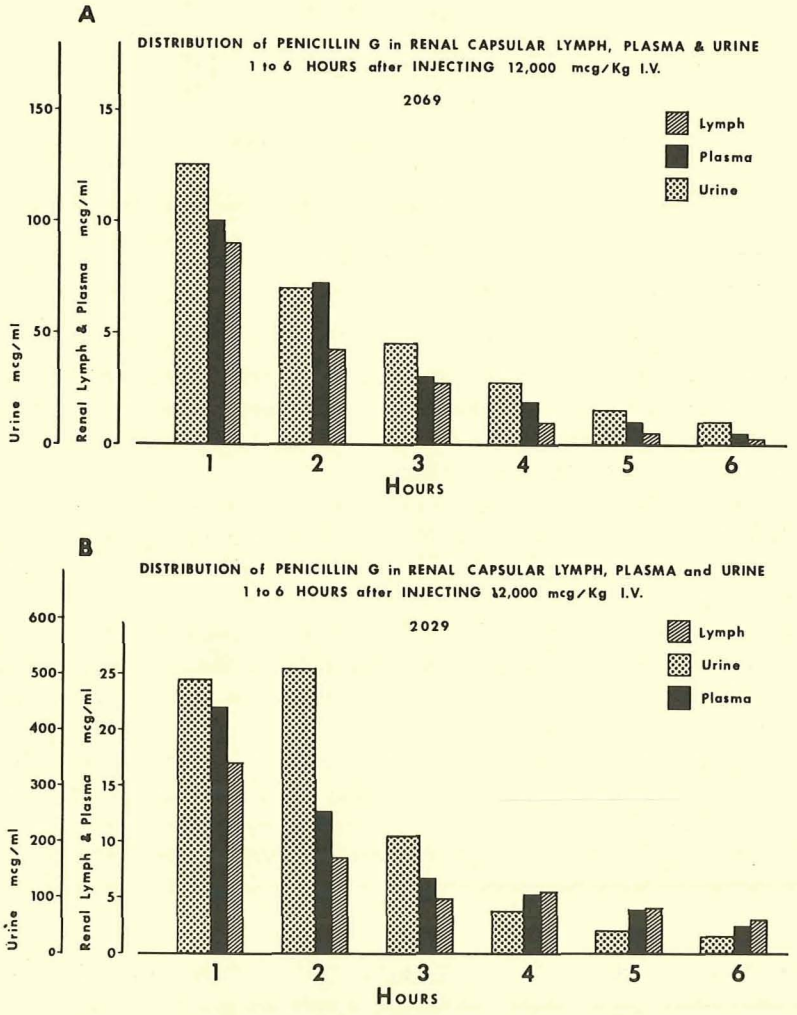

FIG. 2. *A*, Distribution of penicillin G in renal capsular lymph, plasma, and urine. *B*, Distribution of penicillin G in renal capsular lymph, plasma, and urine.

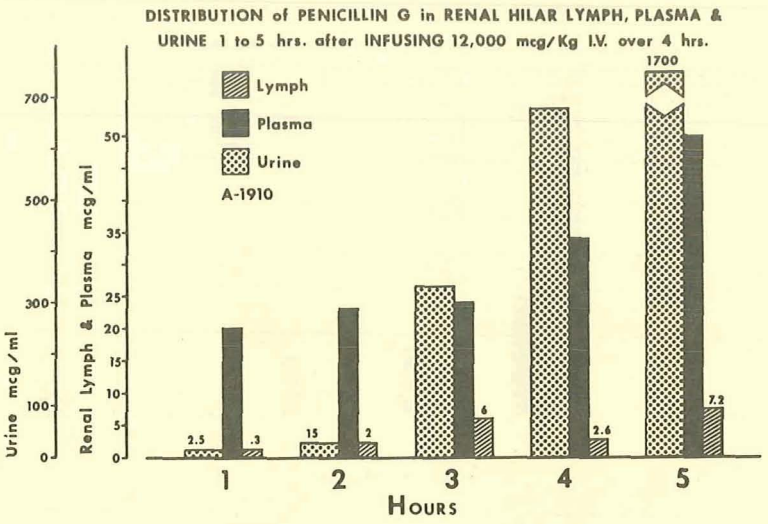

FIG. 3. 4-hr infusion of penicillin G. Comparisons made of renal hilar lymph, plasma, and urine.

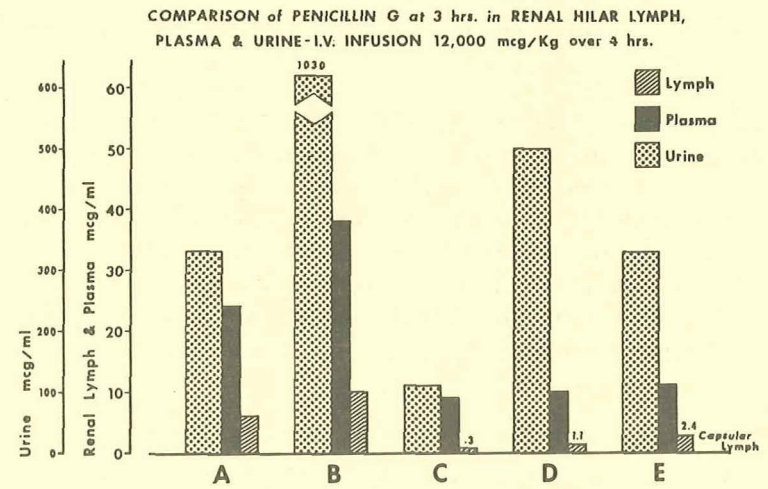

FIG. 4. Penicillin G concentrations compared in renal hilar lymph, plasma, and urine of four animals.

renal hilar lymph, plasma, and urine of four animals. Hilar lymph concentrations are $\frac{1}{5}$ to $\frac{1}{10}$ of the corresponding plasma levels 3 hr after a slow intravenous infusion. Urinary concentrations range from 100 to 1,030 μg per ml.

Cephalothin was collected from renal lymph in five experiments. A typical illustrative experiment is plotted in Figure 5. Renal lymph samples exceed or approximate the corresponding plasma samples 1 to 5 hr after infusion. Urinary concentrations range from 164 to 12,000 μg per ml and exceed renal lymph and plasma levels.

Results from two illustrative experiments in five animals receiving cepha-

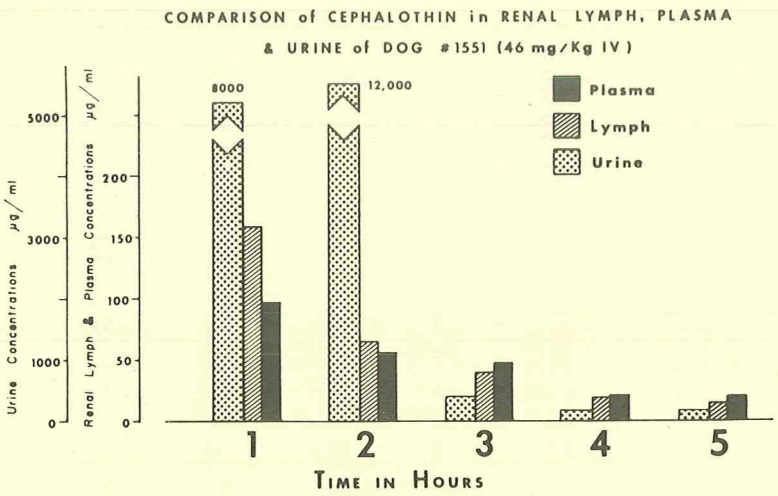

FIG. 5. Cephalothin concentrations in renal lymph, plasma, and urine

loridine are plotted in bar graphs (Fig. 6*A* and *B*). The renal lymph concentrations exceed the corresponding plasma samples 1 to 3 hr after rapid infusion of the antibiotic. Urinary concentrations of cephaloridine are variable in both experiments but exceed lymph and plasma levels.

Nalidixic acid is plotted bar graph form in Figure 7. Renal lymph and plasma concentrations in four experiments are listed. Plasma levels exceed renal lymph concentrations approximately 3 hr after gastric infusion.

An illustrative experiment for nalidixic acid is plotted (Fig. 8). Urinary distribution is divided into free and conjugated nalidixic acid. Urinary levels of free nalidixic acid are 50 to 110 μg per ml 2 to 3 hr after infusion.

Figure 9 is a bar graph depicting the distribution of nitrofurantoin in renal lymph and coresponding plasma samples. Renal lymph levels exceed plasma by two- to three-fold.

DISCUSSION

Verwey and co-workers (7, 8) have previously reviewed the problems of penicillin transport. A model for diffusion demonstrating flux between vascular and extravascular compartments has been described. Protein binding of penicillin G was approximately 50 per cent. Protein binding of penicillin G in lymph fluid however, was significantly depressed. Nonetheless, concentrations of unbound penicillin in the plasma appreciably affected the concentrations of free penicillin diffusing into interstitial tissues. Distribution of penicillin G in plasma, lymph, and urine was affected by the speed of infusion as seen by our data.

The renal lymph levels observed after infusing penicillin G, cephalothin, and cephaloridine raise a number of new questions. Protein binding among the three structurally related antibiotics is variable; these differences would appear to be an attractive explanation for the concentrations found in renal lymph. Penicillin G and cephalothin are bound to protein by approximately

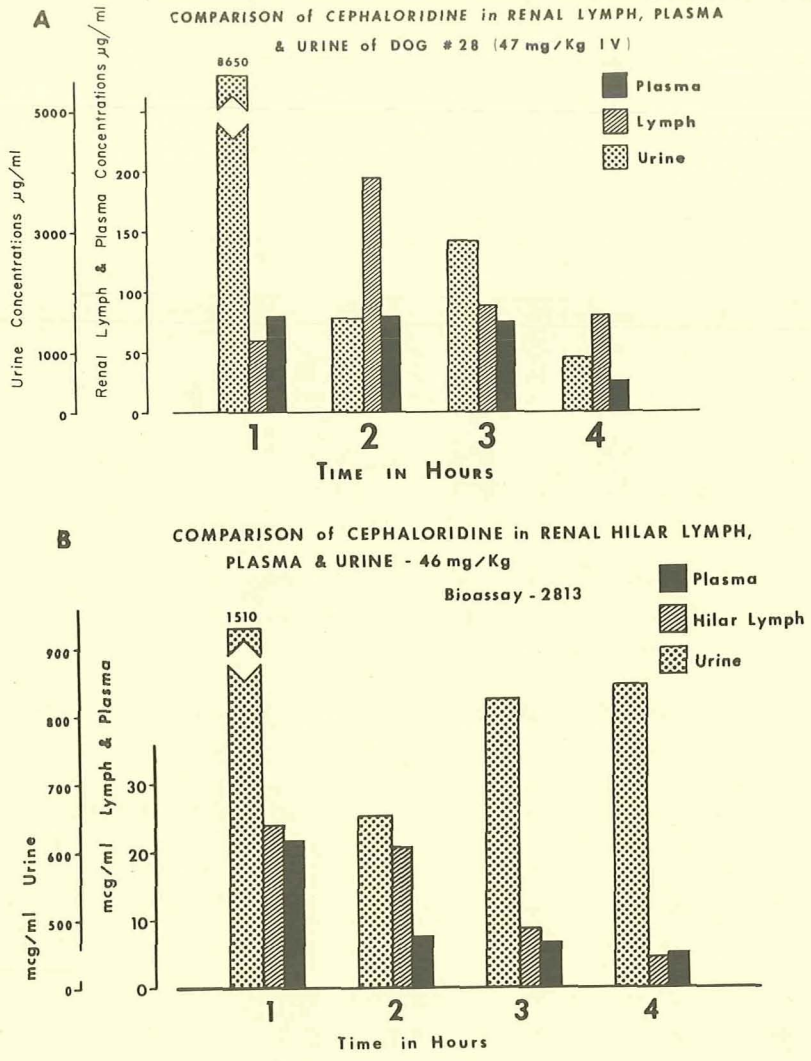

FIG. 6. *A*, Distribution of cephaloridine in renal capsular lymph, plasma, and urine. *B*, Distribution of cephaloridine in renal hilar lymph, plasma, and urine.

the same percentages, 40 to 50 per cent. Cephaloridine, however, is not bound significantly to protein. Renal lymph plasma ratios of the three antibiotics were compared during corresponding time intervals. Animals injected with cephaloridine showed a higher renal lymph to peripheral plasma ratio than penicillin G animals. Cephalothin and penicillin G appeared to be handled in similar fashion by the renal tubules.

Apparently the greater structural similarity of the cephalosporins—cephalothin and cephaloridine—cannot account for the concentrations found in renal lymph fluid when compared with blood. Welles and associates (9) compared the renal clearance of cephaloridine with the simultaneous clearance of exogenous

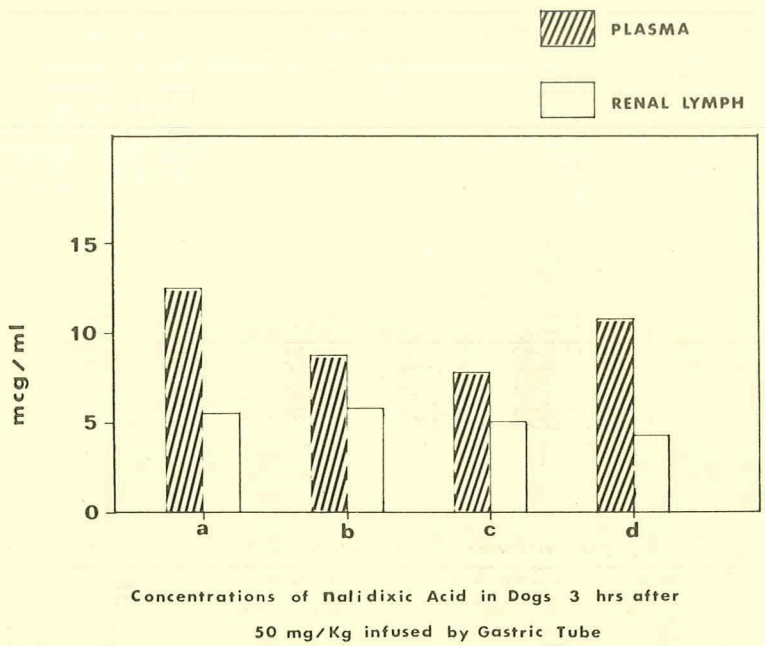

FIG. 7. Concentrations of nalidixic acid in renal lymph and plasma 3 hr after gastric infusion.

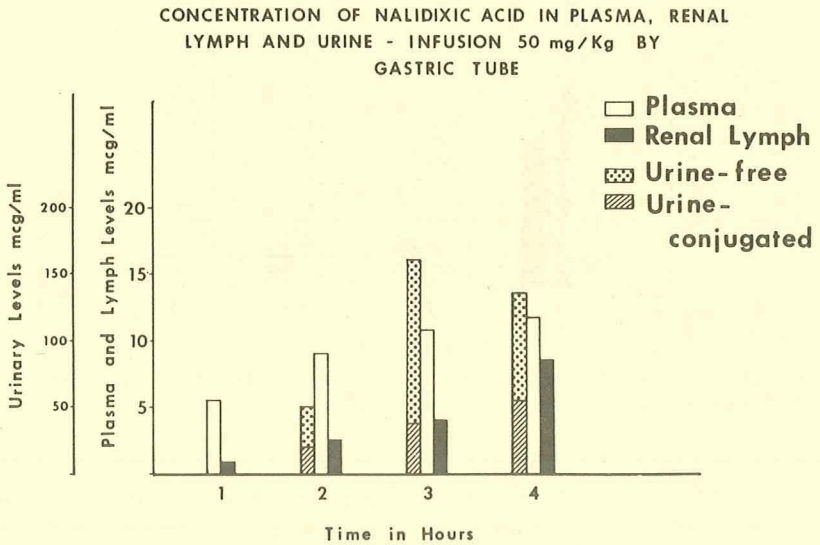

FIG. 8. Distribution of nalidixic acid in renal lymph, plasma, and urine

creatinine in dogs. The clearance rates of creatinine and cephaloridine were similar, suggesting that renal elimination of cephaloridine results from glomerular filtration. Administration of probenecid did not affect the clearance of creatinine or cephaloridine in these same animals.

The renal handling of cephalothin however, resembled the tubular secre-

NITROFURANTOIN

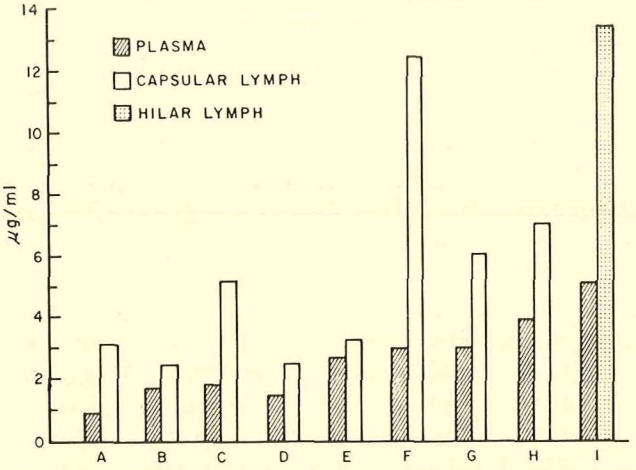

FIG. 9. Distribution of nitrofurantoin in renal lymph and corresponding plasma 2 hr after gastric infusion, 7 mg per kg.

TABLE 1

Dog No.	Drug	Date	Renal Vein pH	Femoral Artery pH	Capsular Lymph pH
827	None	2/16/66		7.265	7.460
257	Penicillin G	3/15/66		7.44	7.665
273	None	3/17/66	7.385	7.405	7.480
792	Penicillin G	4/26/66	7.290	7.285	7.590
891	Tetracycline	5/3/66	7.320	7.300	7.665
849	Cephaloridine	5/10/66	7.530	7.505	7.680
852	Tetracycline	5/11/66	7.350	7.345	7.588
979	None	5/24/66	7.375	7.370	7.375
1111	Cephalothin	6/16/66	7.335	7.349	7.530
1186	Cephalothin	2/21/66	7.500	7.500	7.850
1239	None	7/5/66	7.100	7.150	7.280
1286	Cephalothin	7/11/66	7.600	7.600	7.700
1503	Cephalothin	8/1/66	7.280	7.305	7.450
1551	Cephalothin	8/12/66	7.445	7.256	7.375
	None	8/18/66	7.401	7.388	7.550
1684	None	8/23/66	7.550	7.475	7.790
1643	Chlortetracycline	8/29/66	7.285	7.305	7.500
1630	None	8/30/66	7.500	7.450	7.560
2029	Penicillin G	9/2/66	7.289	7.340	7.589
2069	Penicillin G	9/26/66	7.385	7.375	7.480
1251	Oxytetracycline	7/18/66	7.650	7.600	7.620
1430	Oxytetracycline	7/20/66	7.420	7.402	7.600

tion curves of penicillin G. Cephalothin is secreted by the renal tubules. Tubular secretion of this therapeutic agent, like penicillin G, can be blocked by probenecid. Lee and his co-workers (10) reported a decrease in the cephalothin-creatinine clearance ratio from 1.8 during the control phase to 1.0 when probenecid was administered.

Recent findings by Curry *et al.* (11) bring into focus still another factor when cephaloridine is considered. These authors demonstrated increased activity of tritium-labeled cephaloridine in the renal interstitium of the canine kidneys, suggesting the possibility of tubular reabsorption of this antibiotic. The antibiotic was compared with nitrofurantoin, a urinary antiseptic whose handling characteristics within the kidney are well known. C-14-labeled nitrofurantoin was also found in higher concentrations within the renal interstitium, lymph fluid.

The foregoing observations would suggest that protein binding of antibiotics may play an important role in renal tubular excretion. Tubular reabsorption and passive diffusion into renal lymph fluid of cephaloridine may occur during the early intervals after intravenous administration.

Underway in our laboratory are studies to determine the renal interstitial distribution of C-14-labeled cephalothin, cephaloridine, and structurally related antibiotics. Only when such experiments are coupled with renal lymph cannulation studies can a much clearer explanation be given of the manner in which kidneys handle related antibiotics. Also underway are studies evaluating the effects of probenecid on tubular secretion of penicillin G and cephalothin.

Nalidixic acid, in contrast to nitrofurantoin, has a higher plasma to lymph ratio. Nitrofurantoin (7 mg per kg) was found in higher therapeutic concentrations in renal lymph than in plasma. Conjugation of nalidixic acid also curtails some urinary activity of this antiseptic.

Worth emphasizing is the careful selection of antibiotics for the treatment of acute pyelonephritis. If the bacteria are sensitive to penicillin G and the cephalosporins, and the foci are located in the renal interstitium, then cephaloridine would appear to be a reasonable choice. More studies are indicated, however, before this important distinction can be made.

Urinary antiseptics are useful in the treatment of bacteriuria. When one considers the distribution of antiseptics, the concentrations of nitrofurantoin in renal lymph appear significant. The choice in selecting these agents should be made on the basis of careful bacterial identification and tube dilution sensitivities. Of some importance is the level of free unconjugated antimicrobial agents in urine.

REFERENCES

1. Stamey, T. A., Govan, D. E., and Palmer, J. M.: The localization and treatment of urinary tract infections: The role of bactericidal urine levels as opposed to serum levels. Medicine *44:* 1–36, 1965.
2. Cockett, A. T. K., Roberts, A. P., and Moore, R. S.: Significance of antibacterial levels in the renal lymph during treatment for pyelonephritis. J. Urol., *95:* 164, 1966.

3. Cockett, A. T. K., Moore, R. S., and Kado, R. T.: The renal lymphatics and therapy of pyelonephritis. Brit. J. Urol., *37:* 650, December 1965.
4. Katz, Y. J., Cockett, A. T. K., and Moore, R. S.: Microbiological activity of renal lymph containing antibacterials, p. 742. In *Progress in Pyelonephritis.* H. Kass (Editor). F. A. Davis Company, Philadelphia, 1965.
5. Cockett, A. T. K., Kado, R. T., Roberts, A. P., and Moore, R. S.: The renal lymphatics: An active fluid transport system. In *Proceedings of International Symposium on Lymphology, Zurich, Switzerland 1966.*
6. McChesney, E. W., Froelich, E. J., Lesher, G. Y., Crain, A. V. R., and Rosi, D.: Absorption, excretion and metabolism of a new antibacterial agent, naladixic acid. Toxic. Appl. Pharmacol., *6:* 292, 1964.
7. Verwey, W. F., Williams, H. R., Jr., and Kalson, C.: Penetration of chemotherapeutic agents into tissues. Antimicrob. Agents Chemother., 1016–1024, 1965.
8. Verwey, W. F., and Williams, H. R., Jr.: Binding of various penicillins by plasma and peripheral lymph obtained from dogs. Antimicrob. Agents Chemother., 484–491, 1962.
9. Welles, J. S., Gibson, W. R., Harris, P. N., Small, R. M., and Anderson, R. C.: Toxicity, distribution and excretion of cephaloridine in laboratory animals. Antimicrob. Agents Chemother., 863–869, 1965.
10. Lee, C.-C., Herr, E. B., Jr., and Anderson, R. C.: Pharmacological and toxicological studies on cephalothin. Clin. Med. *70:* 1963.
11. Currie, G. A., Little, P. J., and McDonald, S. J.: The localisation of cephaloridine and nitrofurantoin in the kidney. Nephron, *3:* 282, 1966.